*Environmental Health Perspectives*
*Vol. 19, pp. 159–164, 1977*

# Metabolic Interrelationships Between Arsenic and Selenium

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**In 1938, Moxon discovered that arsenic protected against selenium toxicity. Since that time it has been shown that this protective effect of arsenic against selenium poisoning can be demonstrated in many different animal species under a wide variety of conditions. Antagonistic effects between arsenic and selenium have also been noted in teratologic experiments.**

**Early metabolic studies showed that arsenic inhibited the expiration of volatile selenium compounds by rats injected with acutely toxic doses of both elements. This was puzzling since pulmonary excretion had long been regarded as a means by which animals could rid themselves of excess selenium. However, later work demonstrated that arsenic increased the biliary excretion of selenium. Not only did arsenic stimulate the excretion of selenium in the bile, but selenium also stimulated the excretion of arsenic in the bile. This increased biliary excretion of selenium caused by arsenic provides a reasonable rationale for the ability of arsenic to counteract the toxicity of selenium, although the chemical mechanism by which arsenic does this is not certain. The most satisfactory explanation is that these two elements react in the liver to form a detoxication conjugate which is then excreted into the bile. This is consistent with the fact that both arsenic and selenium each increase the biliary excretion of the other. Several other metabolic interactions between arsenic and selenium have been demonstrated *in vitro*, but their physiological significance is not clear.**

**Although arsenic decreased selenium toxicity under most conditions, there is a pronounced synergistic toxicity between arsenic and two methylated selenium metabolites, trimethylselenonium ion or dimethyl selenide. The ecological consequences of these synergisms are largely unexplored, although it is likely that selenium methylation occurs in the environment.**

**All attempts to promote or prevent selenium deficiency diseases in animals by feeding arsenic have been unsuccessful.**

**Over 30 years ago it was suggested that industrial hygienists use arsenic as a tonic to prevent or cure selenium poisoning in workers exposed to this hazard. Organic arsenical feed additives were tried as partial antidotes against selenium poisoning in livestock raised in seleniferous agricultural areas but were not found to be practical.**

## Historical Background

In the 1930's, workers at the South Dakota Agricultural Experiment Station discovered that the toxic principle in some plants grown in certain regions of the Great Plains that caused the malady known as "alkali disease" was selenium (*1*). In experiments with rats they showed that at the concentrations used selenium was the only element tested that produced severe liver pathology (*2*). While studying the toxicity of selenium in combination with several other elements, Moxon found that arsenic had a remarkable ability to protect against the toxicity of selenium (*3*). From this original observation, a wealth of experimentation has been generated in an attempt to explain this metabolic antagonism between arsenic and selenium and also to search for other biological systems in which arsenic and selenium might interact.

## Effects of Arsenic on Selenium Toxicity

Once the protective effect of arsenic against selenium toxicity was established, additional work was initiated to determine the specificity of the arsenic effect. Several different elements were given

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as their water-soluble salts in the drinking water and were found to be inactive in preventing selenium poisoning, including fluorine, molybdenum, chromium, vanadium, cadmium, zinc, cobalt, nickel, uranium, lead, and gallium (*4–6*). Only arsenic as sodium arsenite gave full protection against the liver damage and growth depression caused by a diet containing selenium from seleniferous wheat (*4*). Some other elements, such as tungsten, bismuth, germanium, and antimony (as the trichloride fed in the ration but not as sodium antimoniate) showed a partial protective effect against selenium (*4–7*).

Many different forms of arsenic have been tested for their ability to counteract selenium poisoning. Sodium arsenite and sodium arsenate were equally effective in preventing the toxicity of selenium but the insoluble arsenic sulfides, $AsS_2$ and $AsS_3$, were essentially inactive (*5*). Several organic arsenicals have shown partial protective action against selenosis including the formerly used antisyphilitic drugs, neoarsphenamine and sulfarsphenamine (*6*), and the currently used livestock feed additives, arsanilic acid and 3-nitro-4-hydroxyphenylarsonic acid (*8*). Sodium methyl arsenate and calcium methyl arsonate had little or no beneficial effect versus selenium poisoning (*9*).

Arsenic compounds have been shown to protect against a variety of different forms of selenium. Sodium arsenite, for example, was active against selenium as seleniferous wheat, sodium selenite, or selenocystine (*5*). Arsenic has also been demonstrated to protect against the toxic effects of selenomethionine (*10*).

The protective effect of arsenic has been observed in a wide variety of species including rats (*4*), dogs (*11*), swine (*12, 13*) and cattle (*14, 15*). In poultry, arsenic not only decreased the growth inhibition caused by excess selenium (*16*) but also improved the poor hatchability of eggs from selenized birds (*17*), apparently by reducing the amount of the element that is incorporated into the egg (*18*). The mechanism by which arsenic prevents selenium poisoning remained unexplained for a long time. It had been shown that oral administration of arsenic detoxified selenium regardless of whether the arsenic was given in the diet or in the drinking water (*5*). This gave rise to the suggestion that arsenic might decrease the toxicity of selenium by combining with it in the gastrointestinal tract, thereby decreasing the absorption of the element. But Moxon et al. later showed that arsenic could prevent selenium poisoning, even when compounds of both elements were injected subcutaneously (*19*). This finding proved that arsenic did not act by interfering with the gastrointestinal absorption of selenium.

In experiments designed to clarify the mechanism by which arsenic protects against selenium toxicity, Kamstra and Bonhorst noted that arsenic decreased the expiration of volatile selenium compounds when rats were injected with acutely toxic doses of both elements (*20*). The biosynthesis of the volatile product, dimethyl selenide, from selenite has been studied in some detail at the subcellular level by Ganther and associates (*21*). The reaction pathway apparently consists of reduction of the selenite to the selenide oxidation state followed by methylation by methyl transferase enzymes. The methyl transferase in the microsomal fraction of the liver is very sensitive to arsenite and this sensitivity may account for the ability of arsenic to inhibit the production of volatile selenium compounds.

But the tendency of arsenic to reduce selenium volatilization did not seem to be consistent with a protective effect of arsenic in selenium poisoning since the formation of volatile selenium compounds had long been regarded as a detoxification process by which an animal ridded itself of excess amounts of selenium (*22*). In earlier work, Ganther and Baumann had carried out total metabolic studies on rats injected with subacute doses of arsenic and selenium and found that, in addition to blocking the production of volatile selenium compounds, arsenic markedly decreased the retention of selenium in the liver and increased the amount of selenium appearing in the gastrointestinal tract (*23*). This finding was expanded upon by Levander and Baumann (*24*), who showed that, as the dose of arsenic given to the rat was varied, there was an inverse relationship between the amount of selenium retained in the liver and the amount appearing in the gastrointestinal tract (Table 1). This relationship suggested that arsenic might act by promoting the biliary excretion of selenium, and experiments in rats or guinea pigs with cannulated bile ducts demonstrated that this was so (*25*). Animals injected with both arsenic and selenium excreted ten times as much selenium into the bile during a 3-hr collection period as animals

**Table 1. Distribution of selenium in rats given various doses of arsenic.[a]**

| Dose of arsenite, mg As/kg | Proportion of the dose of selenium, % | |
|---|---|---|
| | In liver | In gastrointestinal contents plus feces |
| 0.0 | 24.9 ± 2.5 | 8.7 ± 0.3 |
| 1.0 | 17.8 ± 2.0 | 11.2 ± 1.4 |
| 2.0 | 13.9 ± 1.4 | 25.4 ± 6.2 |
| 3.0 | 8.0 ± 0.9 | 22.4 ± 2.1 |
| 5.0 | 8.6 ± 1.0 | 25.8 ± 0.5 |

[a]Data of Levander and Baumann (*24*); all animals received 2 mg Se/kg as sodium selenite 10 min after injection with saline or sodium arsenite; length of experiment was 10 hr.

injected with selenium alone (Table 2). There was much less selenium retained in the livers of the arsenic-treated rats than in the controls, but there was no difference in the amount of selenium appearing in the gastrointestinal contents between these two groups of animals with cannulated bile ducts. Increased volume of bile excreted by the arsenic-treated rats could not account for the increased level of selenium in the bile of these animals.

This effect of arsenic in stimulating the biliary excretion of selenium was observed over a wide range of dosages and under different experimental conditions. Sodium arsenite was by far the most active form of arsenic in enhancing the biliary excretion of selenium although sodium arsenate was

**Table 2. Effect of arsenic on the biliary excretion of selenium.[a]**

| | Proportion of the dose of selenium, % | |
|---|---|---|
| | Saline only | Selenite |
| Bile | 4.0 ± 0.4 | 40.8 ± 7.2 |
| Liver | 51.3 ± 3.0 | 20.9 ± 3.0 |
| Gastrointestinal contents | 1.7 ± 0.3 | 1.5 ± 0.3 |
| Bile volume (ml) | 3.0 ± 0.2 | 3.8 ± 0.5 |

[a]Data of Levander and Baumann (*25*); all animals received 0.5 mg Se/kg as sodium selenite 10 min before injection with either saline or 1 mg As/kg as sodium arsenite.

also reasonably effective. Various organic arsenicals, such as arsanilic acid or 3-nitro-4-hydroxyphenylarsonic acid, were much less potent. Arsenite also increased the biliary excretion of selenium when the latter was administered in the form of selenate but had no effect on the biliary excretion of sulfur given as sulfate. Just as arsenite stimulated the excretion of selenium into the bile, so did selenite stimulate the excretion of arsenic into the bile (Table 3). Arsenic was quite specific in increasing the biliary excretion of selenium since mercury, thallium, and lead had no effect in this regard, even though both mercury and thallium blocked the formation of volatile selenium compounds (Table 4). Dialysis experiments revealed that much of the selenium in bile from arsenictreated rats was loosely bound to macromolecules since only 37% of the biliary selenium was dialyzable against buffered saline but addition of $10^{-3}M$ glutathione to the dialysis medium increased the dialyzable fraction to 73% (*25*).

**Table 3. Effect of selenium on the biliary excretion of arsenic.[a]**

| | Proportion of the dose of arsenic, % | |
|---|---|---|
| | Saline only | Arsenite |
| Bile | 9.2 ± 1.2 | 18.3 ± 1.7 |
| Liver | 19.0 ± 1.5 | 11.0 ± 0.6 |
| Gastrointestinal contents | 1.6 ± 0.2 | 1.7 ± 0.2 |
| Bile volume (ml) | 1.17 ± 0.07 | 1.22 ± 0.14 |

[a]Data of Levander and Baumann (*25*); all animals received 1.0 mg As/kg as sodium arsenite 10 min after injection with either saline or 0.5 mg Se/kg as sodium selenite; bile was collected for 1 hr.

**Table 4. Effect of arsenic and heavy metals on the biliary excretion of selenium.[a]**

| | Proportion of the dose of selenium, % | |
|---|---|---|
| | Bile | Liver |
| None | 1.1 ± 0.2 | 28.6 ± 1.0 |
| $NaAsO_2$ | 21.2 ± 4.4 | 10.6 ± 1.7 |
| $HgCl_2$ | 1.5 ± 0.3 | 28.8 ± 1.5 |
| $Tl(C_2H_3O_2)$ | 0.9 ± 0.2 | 29.3 ± 2.9 |
| $Pb(C_2H_3O_2)_2 \cdot 3H_2O$ | 1.0 ± 0.1 | 28.9 ± 0.7 |

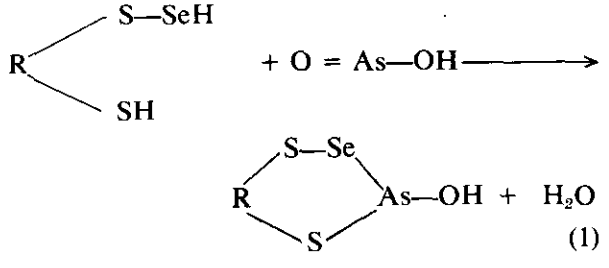
[a]Data of Levander and Argrett (*26*); all animals received 0.5 mg Se/kg as sodium selenite 10 min before injection with either saline or 1 mg of the test element/kg; length of experiment was 1 hr.

Thus, it appears that the increased biliary excretion of selenium caused by arsenic provides, on a physiological level, a reasonable explanation for the ability of arsenic to counteract the toxicity of selenium. Although some workers have not been able to find any effect of arsenic on the fecal or urinary excretion of selenium when both elements were given at low dose levels (*27*), others have shown that selenium levels were decreased in the livers of animals chronically poisoned with selenium and treated with arsenic as compared to control animals given selenium alone (*4, 16, 26*). This latter observation agrees with the hypothesis that arsenic clears selenium from the liver which in many species is the primary target organ of selenium poisoning.

The precise chemical mechanism by which arsenic detoxifies selenium is still unknown, although several possibilities have been discussed (*25*). The most appealing explanation is that selenium and arsenic react in the liver to form a detoxification conjugate which is then excreted into the bile. Such an explanation would seem to be one that is consistent with the fact that arsenic and selenium each increase the biliary excretion of the other. How or whether this mechanism is related to the inhibitory effect of arsenite on the methyl transferase responsible for the formation of dimethyl selenide is unknown. However, if the methyl transferase were blocked, excessive levels of hydrogen selenide might be generated in the liver, which then could react with any arsenite present in a manner akin to the reaction between arsenite and thiols. Such a selenoarsenite might then be the detoxification con-

jugate, discussed above, that is excreted into the bile. Additional research on the chemical forms of arsenic and selenium in bile should resolve this problem.

Although the increased biliary excretion of selenium caused by arsenic provides, at least in the opinion of this author, the most reasonable explanation for the mechanism by which arsenic protects against selenium toxicity, we should not ignore the possibility that other metabolic interactions between selenium and arsenic may also have roles. For example, early work from South Dakota showed that hepatic succinic dehydrogenase levels were markedly depressed in rats poisoned with selenium, but this depression was dramatically relieved in animals also treated with arsenic (*28*). Of course, this could be merely a secondary phenomenon that is related to the overall well-being of the animals, but Levander and co-workers showed that the glutathione-induced swelling of rat liver mitochondria stimulated by selenite could be powerfully inhibited by arsenic, cadmium or mercury (*29*). But, unlike cadmium or mercury, arsenic had little or no inhibitory effect on the selenium-catalyzed reduction of cytochrome c by glutathione in a chemically defined model system (*30*). This suggests that the arsenite had its effect in the mitochondrial system by reacting with a peculiar grouping of ligands that were not present in the chemical model system. It was suggested that the peculiar grouping might be a selenopersulfide in close proximity to a sulfhydryl ligand (*30*). Thus, an inhibitory complex would be formed as shown in eq. (1). Additional research is needed to clarify the possible role of this arsenic/selenium antagonism in metabolism.




(1)

Other possible arsenic/selenium interactions of metabolic significance which should not be overlooked are based on the chemical parameter concept developed by Matrone and Hill (*31*). When this concept is applied to oxyanions, the most important parameters to be considered are the anion orbital configuration and the number of $\pi$-*d* bonds. On this basis, it was predicted, and experimentally verified, that selenate could partially prevent the uncoupling of oxidative phosphorylation caused by arsenate (*32*). This metabolic antagonism may be explained by the reciprocal inhibition of uptake of these two anions by mitochondria. Similar experiments were carried out in yeast by Bonhorst in an attempt to use anion antagonisms as indicators of the mechanism of selenium toxicity (*33*). More work is required to determine whether these *in vitro* phenomena contribute to the protective effect of arsenic in selenium poisoning.

Although the above discussion clearly demonstrates that arsenic decreased selenium toxicity under most experimental conditions, there are certain specific situations in which arsenic increases selenium toxicity. Obermeyer et al. have shown (*34*) that poisoning by trimethylselenonium chloride, a compound of relatively low toxicity compared to many other selenium compounds, is markedly increased by simultaneous injection with arsenite. A similar potentiating effect was seen when arsenite was injected along with dimethyl selenide, a rather innocuous selenium compound (*35*), and one that is generally considered a detoxification product of selenium metabolism (*22*). This highly synergistic toxicity between arsenic and methylated selenium derivatives is reminiscent of that reported by Parizek et al. between mercury and dimethyl selenide (*36*). The mechanism of the synergism in either of these two cases is unknown, but in light of the likely methylation of selenium in the environment (*37*) these metabolic interrelationships are worthy of much additional study.

## Effects of Arsenic and Selenium on Teratogenesis

An intriguing example of the arsenic/selenium antagonism was provided by the work of Holmberg and Ferm (*38*), who showed that selenium decreased the teratogenic toxicity of arsenic in hamsters when salts of these two elements were injected simultaneously. On the other hand, Palmer et al. (*39*) found that arsenite decreased the toxic effect of several selenium compounds to chick embryos. Arsenite even decreased the toxicity of trimethylselenonium ion to chick embryos, even though these two compounds have a pronounced synergistic toxicity in rats.

The mechanism by which selenium decreases the embryotoxicity of arsenic and vice versa is not known but some of the metabolic relationships discussed above might be involved. On the other hand, Walker and Bradley (*40*) found interacting effects of sodium arsenate and selenocystine on chromosomal crossing over in fruit flies that they related to the

possible incorporation of arsenate and selenocystine into DNA and chromosomal protein, respectively. However, that interaction was a synergistic one, so that it could not explain the arsenic/selenium antagonism described by Palmer et al. and Holmberg and Ferm.

## Effects of Arsenic on Selenium Deficiency

Since arsenic had been shown to decrease the retention of selenium in the tissues, it was logical to determine whether arsenic could increase the nutritional deficiency of selenium in animals fed diets low in selenium. However, all attempts to promote selenium deficiency in animals by feeding arsenic compounds have thus far been unsuccessful. The addition of arsanilic acid and *p*-ureidobenzenearsonic acid to a low selenium diet did not increase the incidence or severity of gizzard myopathy in turkey poults (*41*). Neither arsanilic acid (*42*) nor sodium arsenite (*43*) increased the development of liver necrosis in rats fed diets deficient in vitamin E and selenium, and arsanilic acid did not affect the utilization of low levels of selenium by weanling rats (*44*). Finally, supplementation of a selenium-deficient diet with either arsenic trioxide or sodium arsenate had no significant effect on the induction of White Muscle Disease in lambs or on the elevated activities of several plasma enzymes associated with this selenium deficiency disease (*45*).

The metabolic interactions between arsenic and selenium have led some investigators to test arsenic to see if it would prevent selenium deficiency diseases in animals. But Schwarz and Foltz found that sodium arsenate was without effect against liver necrosis in rats (*46*), and Patterson et al. showed that a combination of arsenate and arsenite was inactive in preventing exudative diathesis in chicks (*47*). A preliminary report, which claimed that sodium arsenate significantly reduced the incidence of myopathy in lambs due to selenium deficiency (*48*), has not been confirmed (*45*).

## Practical Considerations

From the industrial hygienist's point of view, the development of a safe form of arsenic that could be used as an antidote against selenium poisoning and vice versa would seem to be a worthwhile goal. This author has made peace with himself in that if he were advised by medical opinion that he had accidently suffered a lethal exposure to either arsenic or selenium he would request that he quickly be given a stiff dose of either selenium or arsenic, respectively, in an attempt to save his life. While this proposal may seem at first irresponsible or absurd, it is not original with this author. Amor and Pringle suggested that a "tonic containing arsenic should be an excellent prophylactic against selenium poisoning in workers exposed to this hazard" over 30 years ago (*49*), when the use of arsenicals in humans as antisyphilitic drugs was still acceptable practice.

From the ecological point of view, the marked synergistic toxicity between arsenic and certain naturally occurring methylated metabolites of selenium is somewhat worrisome. The environmental consequences of such an interaction might be quite similar to those already discussed by Parizek for the marked synergistic toxicity between mercury and methylated selenium derivatives (*36*). As if this picture were not confused enough already, it has recently been stated that arsenic potentiates the beneficial effect of selenium in protecting against methylmercury toxicity (*50*). If these interactions prove nothing else, they demonstrate that environmental or occupational health standards can not be set on a compound by compound or even on an element by element basis. Unfortunately, life is not that simple and much careful thought and research will be needed to sort out the many metabolic interrelationships that occur between arsenic and other elements and their compounds.

From the agricultural point of view, the use of organic arsenicals as a practical means to cure or prevent selenium poisoning in farm animals has been discussed by Olson (*15*). Arsanilic acid and 3-nitro-4-hydroxyphenylarsonic acid were very appealing in this regard since they were already used as feed additives to stimulate the growth of poultry and swine. Although initial trials with arsenicals were encouraging, this did not prove to be a feasible way of controlling selenium poisoning in livestock (*51*).

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